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EFFECTS OF 2 AND 4 MG ATROPINE SULFATE ON VESTIBULAR, COGNITIVE PERFORMANCE, AND OTHER RESPONSES

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The Naval Aerospace Medical Research Laboratory (NAMRL) in conjunction with other DoD laboratories initiated a research program designed to develop standardized tests for assessing and predicting decrements in military performance resulting from the use of chemical defense antidote and pretreatment drugs. This paper focuses only on those elements of the test battery that deal with the measurements of 1) sensory response to motion, balance, and spatial orientation, 2) the ability to coordinate head and eye motions during large gaze shifts, 3) cognitive information processing capabilities, and 4) selected other general tests. It also presents the overall scheduling and test sequence for the entire test battery as applied to the initial four groups of subjects. For the tests described in this report, the only performance decrements due to atropine focused on motor movement functions and a possible effect on central vestibular function. The vestibular portion of the developing test battery appears to be sensitive to the anticholinergic effect of atropine.

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SUMMARY PAGE

THE PROBLEM

The use of chemical weapons by Soviet Forces and their client states has triggered a reanalysis of U.S. chemical warfare defense. Research described in this report is part of a larger effort to develop standardized tests for assessing potential decrements in military performance which could result from treatment with medical chemical defense drugs. This report focuses on preliminary testing of the classic nerve agent antidote atropine sulfate (2 and 4 mg) using selected vestibular, cognitive performance, and other tests.

FINDINGS

The multidisciplinary test battery components described in this report proved to be sensitive to the anticholinergic effect of atropine on responses requiring fine motor movements. An atropine-induced decrement in vestibular function was possibly detected but requires further exploration.

RECOMMENDATIONS

A series of control drugs may help establish a comparison "anchor" on which to judge limited drug effects. For the tests reported herein, alcohol (0.10 mg% blood alcohol) could serve as an excellent comparative baseline. A line commander could intuitively relate various alcohol levels and corresponding levels of the motor (or perceptual) impairment to the same levels of motor impairment resulting from selected drug dosages. In effect, we believe that the development of such comparative baselines would contribute significantly to the operational interpretation of drug-induced performance decrements identified by the multidisciplinary test battery described in this report.

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INTRODUCTION

The Soviet Union has 60,000+ chemical warfare troops, 30,000+ specialized vehicles fitted for chemical warfare operations, and the most extensive chemical warfare arsenal (from mortars to long-range tactical missiles) in the world (1). Information indicates that chemical weapons have been used clandestinely in Cambodia and Afghanistan and openly in the Iran-Iraq war. Recent attempts to reduce the number of intermediate-range nuclear weapons in Europe (INF treaty) have put an even greater emphasis on the potential use of chemical weapons.

In conjunction with other DoD laboratories, the Naval Aerospace Medical Research Laboratory (NAMRL), initiated a research program to develop standardized tests for assessing and predicting decrements in military performance that result from chemical defense antidotes and pretreatment drugs. This report describes results from preliminary testing of the classic antidote atropine sulfate (2 and 4 mg). At the time of testing, specific test procedures had not been completely refined or finalized. The battery of tests used by NAMRL spans five major disciplines: 1) sensory response to motion, balance, and spatial orientation; 2) speech perception and fine motor control associated with speech production; 3) vision and eye tracking capabilities; 4) cardiopulmonary, metabolic, and musculoskeletal function; and 5) cognitive information processing capabilities. Although our primary concern has been the performance of aviation personnel, most of the functions tested are necessary for a wide variety of skills.

A brief review of the results of the overall study has been presented elsewhere (2). This paper focuses only on those elements of the test battery dealing with the measurement of 1) sensory response to motion, balance, and spatial orientation; 2) the ability to coordinate head and eye motions during large gaze shifts; 3) cognitive information processing capabilities; and 4) other selected tests. This report presents the overall scheduling and test sequence for the entire test battery as applied to the initial four groups of subjects.

We do not provide a global review of the atropine literature in this report because of several excellent review papers on atropine effects (3-5) and an abstracted bibliography series concentrating on atropine and related drugs (6). Portions of the multidisciplinary test battery have been used previously to evaluate performance side effects from the drug triazolam (7), and some unpublished, comparative data have been gathered on transdermal scopolamine.

TEST DESCRIPTIONS, METHODS, AND RESULTS

SUBJECTS

The number of subjects participating in each test sequence is shown in Table 1. The 12 subjects in test sequence I consisted of 10 enlisted personnel (9 men, 1 woman) and 2 civilians (1 man, 1 woman). Eleven subjects (2 ensigns, 9 enlisted personnel) participated in test sequence II. Test Sequence III started with 10 enlisted subjects, however 1 individual was rejected because he was taking other medication. Thirteen of the subjects in test sequence IV were U.S. Army helicopter pilots (warrant officers), and the 14th individual was a warrant officer awaiting helicopter training. All

subjects participated on a voluntary basis and had recently passed an extensive physical exam. Subjects requiring corrective lenses were tested with their current lenses or contacts.

TABLE 1. Number of Subjects Participating in Each Test.

Test	Test sequence I (2 mg)	II (2 mg)	III (2 mg)	IV (4 mg)
1. Static balance				
a) Force-balance	12	-	-	14
b) Sharpened Romberg	-	11	9	-
2. Ambulatory balance	-	11	-	-
3. Vestibular suppression	12	-	9	14
4. Gaze function	-	11	-	14
5. Pure-tone audiometry	-	11	9	-
6. Tri-word mod. rhyme				
a) Listen condition	-	11	9	14
b) Speak condition	-	11	9	14
7. Pulmonary function	-	11	9	14
8. Muscular strength and endurance	-	11	9	14
9. Pegboard	-	11	9	-
10. Weight estimate	-	11	-	-
11. Complex tracking	10	-	-	14
12. Matrix rotation	-	11	9	-
13. Interval production	-	11	9	-
14. Pupil diameter	-	11	9	14
15. Near point accommodation	-	11	9	14
16. Near acuity	-	11	9	14
17. Accommodative flexibility	-	11	9	14
18. Dynamic acuity	-	11	9	14
19. Color vision	12	-	-	-
20. Questionnaire				
a) Physiological	12	11	9	14
b) Psychological	-	11	9	14
21. Tilt table	-	-	9	14
22. Walter Reed PAB	-	-	-	14

METHODS

All subjects were tested under both saline and atropine (2 or 4 mg I.M.) conditions (repeated measures design), and in some cases, one or more non-injection baseline data collection periods were also used. For test sequences I, II, and III, subjects received saline or 2-mg atropine injections on Tuesdays and Thursdays (counterbalanced), which allowed at least 48 h for the first injection to clear bodily systems before the second injection. For Test Sequence IV, subjects received saline or 4-mg atropine injections on Fridays and Mondays (counterbalanced), which allowed at least 72 h between injections.

The time following drug administration that each test was conducted is presented in Table 2. Across the four test sequences, we attempted to administer each test at roughly the same time after drug administration.

TABLE 2. Chronological Order of Tests.

	Test	Time after drug (h)
	Test sequence I: 2 mg atropine	
1.	Force-balance	1.00
2.	Complex tracking, matrix rotation, interval production	1.50
3.	Vestibular suppression	2.00
4.	Color vision, quest.-physiol.	2.50
	Test sequence II: 2 mg atropine	
1.	Sharpened Romberg, ambulatory balance, pegboard, weight estimate	1.00
2.	Matrix rotation, interval production	1.50
3.	Gaze function	2.00
4.	Vision tests	2.50
5.	Acoustics tests	3.00
6.	Musculoskeletal tests	3.50
7.	Questionnaire-physiol+psychol	4.00
	Test sequence III: 2 mg atropine	
1.	Sharpened Romberg, ambulatory balance, pegboard	1.00
2.	Matrix rotation, interval production	1.50
3.	Tilt table	2.00
4.	Vestibular suppression	2.50
5.	Gaze function	3.00
6.	Vision tests	3.50
7.	Acoustics tests	4.00
8.	Quest.-physiol+psychol musc. strength + endurance, pulm. func	4.50
	Test sequence IV: 4 mg atropine	
1.	Force-balance	1.00
2.	Gaze function	1.25
3.	Complex tracking	1.75
4.	Walter Reed PAB	2.60
5.	Vestibular suppression	3.00
6.	Acoustics tests	4.10
7.	Vision tests	4.40
8.	Muscular strength + endurance	4.75
9.	Pulmonary function	5.10
10.	Tilt table quest.-physiol+psychol	5.25

STATIC BALANCE--FORCE-BALANCE PLATFORM

Test Description/Procedure

A commercial force-balance platform (Advanced Mechanical Technology, Inc., Computerized Biomechanics Platform System with Computer-Automated Stabilograph software) was used to measure static postural equilibrium of a standing subject (Fig. 1). Four platform variables, identified as Xm, Ym, Rm, and Ao, served as the primary measurement parameters. The variable Xm represented the mean sway amplitude in the X direction (a function of the moment about the Y or anterior/posterior axis); Ym the mean sway amplitude in the Y direction (a function of the moment about the X or lateral left/right axis); Rm the mean radius of sway; and Ao the area included in the sway path. A 30-s measurement period was used for each test condition with data sampled at a 10-Hz rate.

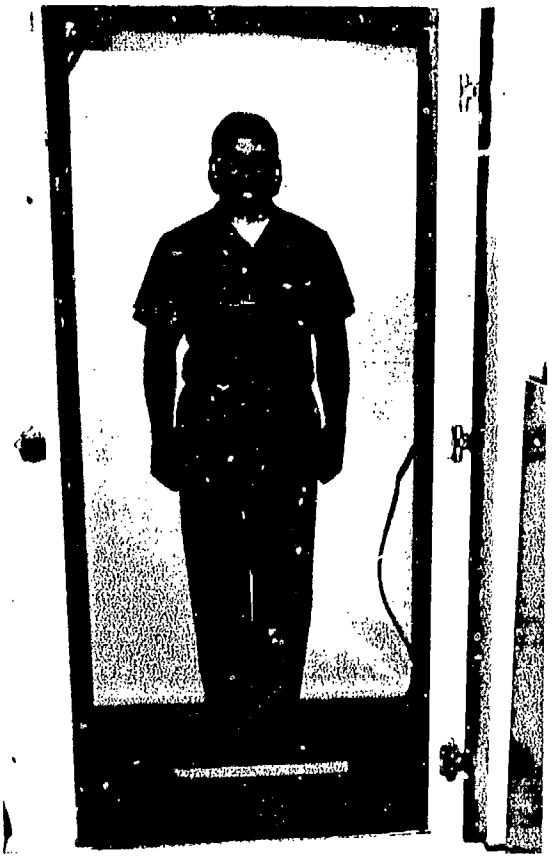

Figure 1. Computerized Biomechanics Platform system used to measure body sway/postural stability.

Results - 2 mg

For the 2-mg atropine dosage, postural equilibrium was measured with the subjects standing erect with feet in a side-by-side position and eyes closed. The measurements were made before and after administration of both the placebo and atropir . Summary data are presented in Table 3. A *t* test for related measures was performed on each of the measurement variables. The .05 level of significance was used on this and all other tests in the battery when specific *p* levels are not reported. There were no statistically significant drug testing effects (*t* (Xm) = .13, *t* (Ym) = 1.98, *t* (Rm) = 1.28, *t* (Ao) = 1.56, *df* for all terms = 11).

TABLE 3. Ataxia Data for the 2-mg Atropine Study: Each Mean for Each Variable Denotes the Ratio of the Measurement Value Obtained 15 min Before/60 min After Drug Administration (*N* = 12).

	Placebo				Atropine			
	Xm	Ym	Rm	Ao	Xm	Ym	Rm	Ao
Mean	0.96	1.14	1.04	1.13	0.98	0.92	0.92	0.91
SD	0.32	0.20	0.26	0.39	0.31	0.34	0.28	0.44

Results - 4 mg

In the 4-mg study, only one testing session was performed following administration of both the placebo and atropine. Each testing session involved one test with eyes open and one with eyes closed. Summary data are displayed in Table 4. We found no significant drug effect for any of the four measurement variables (*t* test for related measures: *t* (Xm) = .09, *t* (Ym) = .329, *t* (Rm) = 1.09, *t* (Ao) = .32, *df* for all terms = 13).

TABLE 4. Ataxia Data for the 4-mg Atropine Study: Each Mean for Each Variable Denotes the Ratio of the Eyes Closed/Eyes Open Values Obtained 60 min After Drug Administration (*N* = 14).

	Saline				Atropine			
	Xm	Ym	Rm	Ao	Xm	Ym	Rm	Ao
Mean	1.69	1.32	1.39	2.74	1.68	1.37	1.49	2.85
SD	0.55	0.43	0.29	0.98	0.42	0.38	0.27	0.96

STATIC BALANCE--SHARPENED ROMBERG

Test Description/Procedure

The Sharpened Romberg test (8) required subjects to stand heel-to-toe with eyes closed and arms folded across their chest (Fig. 2). Four 60-s trials were scored (number of seconds without moving). The completion of any successful 60-s trial terminated the testing, and a maximum score was assigned to any remaining trials (the maximum or best score for all four trials was 240 s). Detailed test procedures and a scoring guideline are described elsewhere (8).

Figure 2. Sharpened Romberg test.

Results - 2 mg

Results from the 2-mg atropine and saline conditions were not significantly different: the mean (± SD) of atropine was 215.8 (± 36.0) s, for saline 215.6 (± 51.5) s, t = .02, df = 19.

AMBULATORY BALANCE

Test Description/Procedure

Ambulatory balance was tested with 2 mg-atropine using the Walk-On-Floor-Eyes-Closed procedure, which is part of a larger Ataxia Test Battery (9). The subject was required to walk on the floor with eyes closed and arms folded across the chest (Fig. 3) for a maximum of 10 heel-to-toe steps without sidestepping. Note that the subject is walking and is not stationary as in Fig. 2. The number of steps properly taken before sidestepping, stopping, opening the eyes, or unfolding the arms was taken as the trial score (maximum of 10 steps per trial). The best 3 out of 5 trials were totaled allowing a maximum score of 30.

Figure 3. Walk-on-floor-eyes-closed test.

Results - 2 mg

The mean scores (± SD) were atropine 27.3 (± 3.8) and saline 29.6 (± 0.9). Using a t test for related measures, atropine significantly reduced ambulatory balance (t = 2.80, df = 19 $p < .05$).

VESTIBULAR SUPPRESSION

Test Description/Procedure

The lightproof Human Disorientation Device (Fig. 4) rotated subjects at 0.025 Hz with a peak velocity of 120°/s. Visual performance was recorded during each 40-s cycle of rotation. A typical order of stimulus presentation is shown in Table 5

TABLE 5. Typical Order for Visual Suppression Test.

	Test Condition	Cycles of rotation
1.	Dark (no visual stimuli)	4
2.	Blue digits/black background	2
3.	Black digits/blue background	2
4.	Break (no rotation for 1 min)	0
5.	Dark (not scored; for adaptation only)	2
6.	Red digits/black background	2
7.	Black digits/red background	2
8.	Break (no rotation for 1 min)	0
9.	Dark (not scored; for adaptation only)	2
10.	White digits/black background	2
11.	Black digits/white background	2
12.	End	-

Figure 4. Human Disorientation Device, on the left, used to measure visual suppression capabilities during sinusoidal rotation.

The dark test condition (#1 in Table 5) preceded the visual stimuli conditions for all subjects. The blue (conditions 2 and 3), red (6 and 7), and white (10 and 11) stimuli conditions were presented in a counterbalanced order (total of six orders of presentation). Within the color conditions, the first six subjects always received the colored digits on the black background first and the black digits on the colored background second. The second set of six subjects always received the black digits on the colored background first. Each set of digits was presented as an 8 by 5 matrix (Fig. 5). The subject was instructed to read and call out as many digits as possible using a left-to-right and top-to-bottom approach. A new set of digits (slide) was presented every 10 s for a total of eight slides per viewing condition.

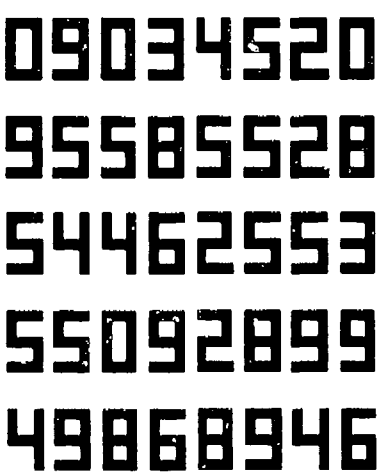

Figure 5. Visual performance matrix (black on white).

The ability to suppress nystagmic eye movements and thus read the display was measured as the number of correct digits reported during each half-cycle of rotation. Performance was scored by partitioning each cycle of rotation (10) into a high velocity time segment (5 s on each side of peak device velocity--both clockwise and counterclockwise rotation) and a low velocity time segment (5 s on each side of zero-device velocity). Note that these performance "windows" are defined on the basis of device rotation/timing and that, in the dark, peak nystagmic beats occur before (phase lead) peak device velocity.

Results - 2 mg

The 2-mg atropine visual performance data are summarized in Table 6. The only statistically significant finding was a drug-related performance decrement within the high velocity data. Results from three-way repeated measures ANOVAs on high and low velocity data are shown in Table 7. Although the effect was not statistically significant, the number of correctly reported digits in the low eye velocity conditions was less under atropine. The lack of a significant drug-induced decrement for low velocity eye movements was probably due to the fact that visual suppression reduced eye movements to the point that blurring was weak or did not occur. As a result of minimal blurring, the subjects may have approached a maximum or ceiling limitation

reflecting optimal performance. Any potential effect of atropine on blurring (central nervous system suppression of nystagmus) was obscured by the weak stimulus during this portion of the rotation cycle.

TABLE 6. Visual Suppression Means (± SD) With 2 mg Atropine.

Drug	Digit color	Background color	Number of correct digits	
			High velocity	Low velocity
Saline	Red	Black	12.91 (8.02)	15.80 (7.38)
	Blue	Black	10.00 (5.54)	13.43 (5.20)
	White	Black	12.86 (6.22)	16.55 (6.27)
	Black	Red	12.49 (6.99)	16.51 (7.37)
	Black	Blue	11.14 (6.20)	14.29 (6.61)
	Black	White	14.10 (7.81)	15.74 (6.37)
Atropine	Red	Black	10.18 (7.68)	14.33 (6.58)
	Blue	Black	7.63 (5.01)	12.25 (5.29)
	White	Black	10.09 (6.67)	14.83 (6.64)
	Black	Red	9.83 (7.24)	14.84 (7.95)
	Black	Blue	8.25 (5.64)	12.60 (5.83)
	Black	White	10.16 (6.26)	14.54 (7.66)

TABLE 7. ANOVA Results with 2 mg Atropine.

ANOVA comparison[a]	High velocity			Low velocity		
	F	df	p	F	df	p
Drug	7.86	1,18	.05	3.00	1,18	NS[b]
Foreground/b'ground	2.08	1,18	NS	0.50	1,18	NS
Digit color	2.02	2,36	NS	2.39	2,36	NS

[a] No significant interactions.
[b] Not significant.

Results - 4 mg

Atropine (4 mg) significantly reduced the number of correctly identified digits for both high and low velocity eye movements (Tables 8 and 9). The portion of this experiment investigating digit color and foreground/background color was part of a separate exploratory research project and is not discussed in detail herein. The atropine-induced decrement in performance, the focus of the present experiment, took place across all the color conditions (Table 8).

TABLE 8. Visual Suppression Means (± SD) with 4 mg Atropine.

Drug	Digit color	Background color	Number of correct digits: High velocity	Number of correct digits: Low velocity
Saline	Red	Black	17.07 (7.20)	19.16 (4.41)
	Blue	Black	10.73 (6.87)	14.00 (6.19)
	White	Black	16.80 (4.97)	20.20 (3.83)
	Black	Red	16.88 (7.71)	21.02 (4.75)
	Black	Blue	12.20 (6.05)	15.50 (4.97)
	Black	White	17.36 (5.20)	19.98 (3.77)
Atropine	Red	Black	8.71 (5.93)	10.95 (6.19)
	Blue	Black	9.91 (5.05)	14.54 (4.78)
	White	Black	11.11 (6.19)	13.98 (5.68)
	Black	Red	8.55 (5.84)	12.25 (7.39)
	Black	Blue	12.25 (6.10)	15.78 (4.56)
	Black	White	11.28 (5.59)	15.16 (5.68)

TABLE 9. ANOVA Results with 4 mg Atropine.

ANOVA comparison	High velocity: F	High velocity: df	High velocity: p	Low velocity: F	Low velocity: df	Low velocity: p
Drug	22.54	1,13	.001	25.86	1,13	.001
Foreground/b'ground	5.25	1,13	.05	7.23	1,13	.05
Digit color	6.69	2,26	.01	6.36	2,26	.01
Drug x color[a]	8.03	2,26	.01	8.25	2,26	.01
F'ground/b'ground x color[a]	4.07	2,26	.05	NS[b]	NS	NS

[a] Only the significant interactions are listed.
[b] Not significant.

GAZE FUNCTION TEST

Test Description/Procedure

This test provides a performance-based measure of head/eye movement coordination during large gaze shifts. The equipment, stimulus conditions, and test protocol are described elsewhere (11). The test involves the sequential presentation of several single alpha characters on one display (alphanumeric light emitting diode) located at eye level 40° to one side of the visual dead-ahead position followed by the presentation of 8 numeric characters on a second display located 40° to the opposite side of the dead-ahead position (Fig. 6). The first display served as a fixation reference where the number and type of alphabetical characters displayed were randomized. The exposure time for display of the numeric data on the second display served as the primary experimental variable. The task required the subject to face the first display, call out the alpha fixation characters as

they appeared, and then rapidly turn his head 80° toward the second display and call out as many of the numeric digits as he could identify. The procedure was then repeated with the fixation characters appearing on the second display and the numeric data on the first display thus requiring a head movement in the opposite direction.

Figure 6. Subject (back exposed) participating in performance-based test of gaze function capabilities.

The main test consisted of a total of 48 trials: 24 trials of left-to-right head movements and 24 of right-to-left movements. Each trial was scored by the number of digits the subject correctly identified. The sequence that the exposure times (500, 750, 1000, and 1250 ms) were presented was randomized, with each exposure time presented the same number of times for each direction of head movement.

Results - 2 mg

A three-way ANOVA was performed based upon drugs (saline versus atropine), direction of head movement (right vs. left), and exposure time (500, 750, 1000, and 1250 ms). A main effect for exposure time was expected and essentially represents the foundation of the test (shorter exposures allow fewer correct responses). The second main effect comparison, the direction of head movement, was not expected to influence test results in vestibularly normal subjects but was designed to detect recent unilateral semicircular canal damage. The a priori statistical approach was to first analyze all the

data using a three-way ANOVA and then to concentrate on the potential saline versus atropine drug effect at the four exposure intervals using t tests for related measures. A similar statistical design was used for the 4-mg data.

For the 2-mg atropine dosage, statistical significance was found for drugs ($F(1, 10) = 11.11$, $p < .01$), exposure time ($F(3, 30) = 252.8$, $p < .001$), and the interaction between direction and time ($F(3, 30) = 4.08$, $p < .05$). A Student t-test analysis of saline versus atropine showed performance degradation due to atropine at 500 ms ($t = 2.91$, $df = 10$, $p < .05$) and at 1000 ms ($t = 2.73$, $df = 10$, $p < .05$).

Results - 4 mg

For the 4-mg dosage, statistical significance was found for drugs ($F(1, 13) = 16.5$, $p < .01$), direction ($F(1, 13) = 4.86$, $p < .05$), exposure time ($F(3, 39) = 419.06$, $p < .001$), and interactions between drugs and direction ($F(1, 13) = 7.96$, $p < .05$) and between drugs and exposure time ($F(3, 39) = 5.09$, $p < .05$). A Student t statistic comparison of saline versus atropine effects showed a performance decrement only at 500 ms ($t = 3.81$, $df = 13$, $p < .005$).

PEGBOARD

Test Description/Procedure

This test of coordinated fine motor movement (Fig. 7) was added to our battery after several subjects in the first test group reported "weakness or clumsiness in arms or legs." The test measures the time needed to accurately place 25 pegs into a pegboard.

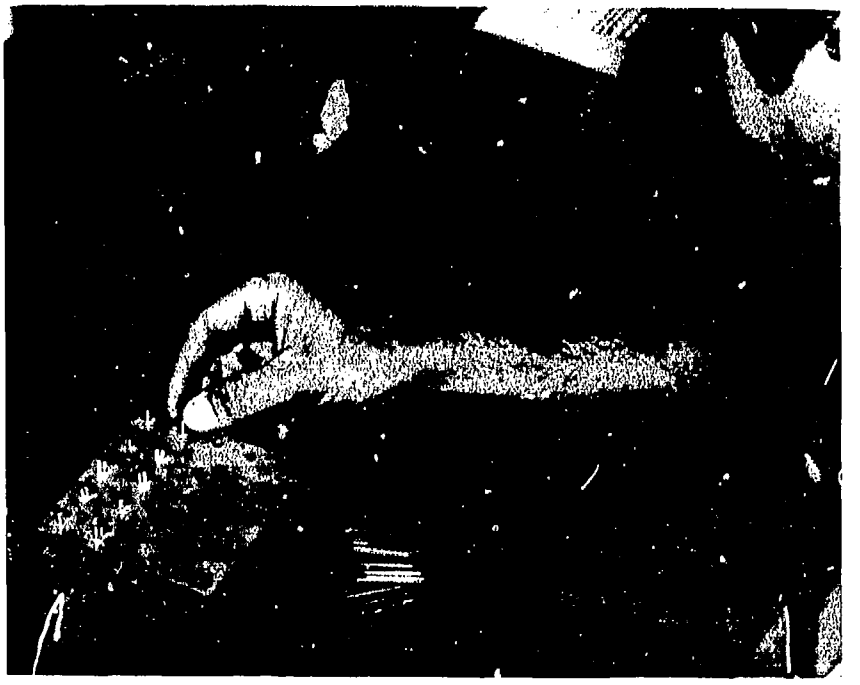

Figure 7. Pegboard Test.

Results - 2 mg

Atropine (2 mg) significantly increased the time required to arrange the 25 pegs with the right hand (t = 5.71, df = 19, $p < .001$) and with the left hand (t = 2.19, df = 19, $p < .05$).

WEIGHT ESTIMATE

Test Description/Procedure

This classic tactile discrimination test (Fig. 8) measures the accuracy of arranging, by weight, 11 light weights (75-125 g) and 11 heavy weights (175-225 g).

Figure 8. Weight Estimate Test.

Results - 2 mg

Atropine (2 mg) did not affect weight discrimination as measured by this procedure (light weights t = 1.67, df = 10, p = NS and heavy weights t = 0.23, df = 10, p = NS).

COMPLEX TRACKING

Test Description/Procedure

A compensatory roll-axis tracking task and a modified visual Sternberg task were used in both single- and dual-task modes during the 2-mg testing, whereas single-task tracking was used during the 4-mg testing. The subject tracked an artificial horizon produced by a low-power (0.43 mW) helium-neon laser projected on a large (8 ft by 8 ft) rear projection screen. The red

(632 nm) laser beam was reflected by a set of galvanometer-driven mirrors using closed-loop, position-mode, scanner amplifiers, and an analog computer. The beam was elongated to form an artificial horizon and rotated to produce roll motion. A random forcing function (Gaussian noise bandwidth 0.15 Hz, amplitude 3.16 V rms) was used to induce roll of the projected horizon (3.16 V produced a 30° deflection). The lengths and configurations of the horizons were varied by inserting circular photographic film "masks" between the laser and the screen, occluding unwanted portions of the horizon.

The subject was seated 1 m in front of the screen as shown in Fig. 9. The subject's chair was equipped with a headrest, and a joystick was attached to the right armrest. A 30° deflection of the joystick produced a 30° deflection of the horizon. The forcing function and the signal from the joystick were fed to a summing amplifier, and a root mean square converter summated root mean square tracking error voltage. Two horizon configurations were used in the 2-mg testing evolution: 1) a long horizon subtending 30° of visual angle, and 2) a short horizon subtending 4°. The 4-mg testing compared three horizon sizes (Fig. 10): small (± 5-10°), medium (± 10-15°), and large (± 15-20°).

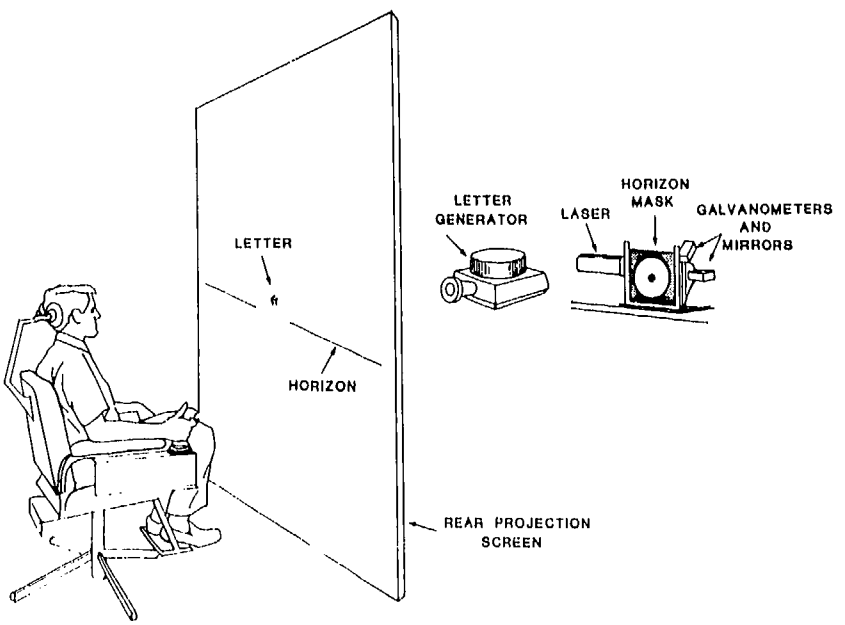

Figure 9. Complex tracking experimental configuration.

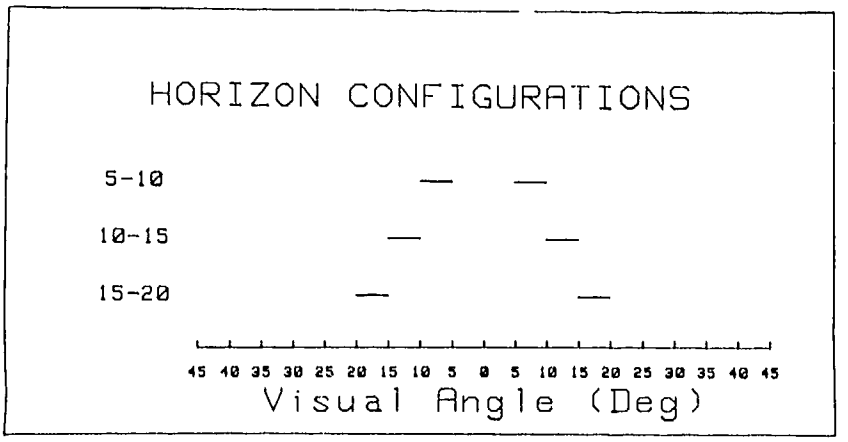

Figure 10. Horizon configurations - 4 mg atropine testing.

A modified visual Sternberg letter identification task was used as a secondary loading task (2 mg only). This task consisted of identification of 8 positive set letters (4 Kanji letters and 4 English letters) mixed with 40 negative set letters (half Kanji, half English, Fig. 11). These letters were presented 30° to the subject's right and left in an alternating fashion. A new letter appeared every 2 s and was visible for 1 s. The subject used two foot-switches to respond to the positive or negative letters. The subject was instructed to maintain his head in a forward-looking position, and a small baffle was placed on the subject's nasion to prevent each eye from seeing the letter in the opposite visual field. The visual baffle was evaluated for use in a potential hemispheric processing experiment and was not related to the results of this experiment.

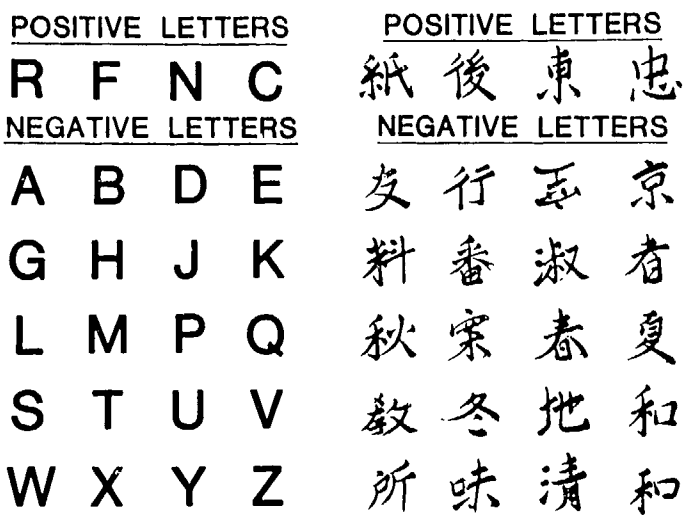

Figure 11. Positive and negative English and Kanji letter sets used in the visual Sternberg task.

Single Task

A short training period was used to teach each subject the positive letters. All subjects were given one practice trial on the single-task baseline trials in the following order: 1) letter identification using the right foot to respond, 2) letter identification using the left foot to respond, 3) tracking the short horizon, and (4) tracking the long horizon. Each of the single-task trials was then performed once. Forty letters were randomly presented during each 80-s letter identification trial with an equal number of positive and negative English and Kanji letters. Subjects were given a 1-min rest between trials, and the order of presentation was counterbalanced across subjects. The same order of testing was used each test day for any given subject. Subject performance measures recorded for each trial included the number of correct, incorrect, and omitted responses and the corresponding response times or root mean square tracking error.

Dual Task

The dual task consisted of compensatory tracking of either the long or short horizon performed simultaneously with letter identification using a right- or left-foot response. Each combination was presented once for a total of four trials. Each 80-s trial was followed by a 1-min rest period with the order of presentation counterbalanced.

The compensatory tracking task, using the laser-projected horizon and various secondary stimuli and response modes, was part of another project and is addressed herein only as it pertains to atropine effects on performance. A complete description of other results can be found elsewhere (11).

Results - 2 mg

Atropine did not affect single- or dual-task compensatory tracking at the 2-mg dose level.

Results - 4 mg

Mean root mean square tracking error for 12 of the 14 subjects receiving 4 mg atropine is shown in Table 10. Two subjects were not included in the statistical analysis because their tracking abilities were extremely poor (> 2 SDs above norm for a group of this composition). Atropine (4 mg) significantly reduced tracking abilities ($F(1, 11) = 26.05$, $p < .001$). Atropine had much less of an effect on the two individuals with poor tracking (possibly a ceiling effect) although when their data were included, the drug effect remained statistically significant ($F(1, 13) = 8.37$, $p < .05$).

TABLE 10. Mean (± SD) Root Mean Square Tracking Error (V).

Test condition	Horizon size		
	Small	Medium	Large
Saline	521 (109)	502 (89)	534 (109)
Atropine	662 (172)	648 (136)	661 (186)

MATRIX ROTATION

Test Description/Procedure

The Matrix Rotation Test evaluates spatial orientation/rotation and short-term memory and is part of the Unified Tri-service Cognitive Performance Assessment Battery (12). A series of 5 by 5 cell matrices are presented (one at a time in the center of the CRT), with five illuminated cells per matrix (Fig. 12). The subject compares successive displays and determines if they are the "same" or "different" from the immediately preceding matrix. The response requires pressing one of two keys designated as "same" or "different." A matrix can be identical to the preceding matrix if exactly the same cells are illuminated but the matrix is rotated 90° to the right, or exactly the same cells are illuminated but the matrix is rotated 90° to the left. Two successive matrices are never presented in exactly the same orientation. Trials are 60 s long with a 30-s break between trials.

Figure 12. Matrix Rotation Test.

The stimulus remains on the screen until the subject responds. The matrix is about 8 cm by 8 cm and is centered horizontally on the screen and slightly above center. The first matrix is displayed at the start of the trial and remains on the screen for 3 s. The second stimulus is presented immediately after the subject's first response, and it remains on the screen until the subject makes another response, et cetera. Subjects respond "same" by pressing a key under their left index finger and "different" by pressing a key under the second finger. Response times are measured from the onset of the stimulus to the response. The keypad is operated by the left hand. For each trial, the percentage errors and average correct reaction time were obtained for each subject.

Results - 2 mg

Atropine (2 mg) did not significantly alter the percentage of correct responses (atropine 86.3%, saline 88.0%, t = 1.80, df = 18) nor did it significantly alter reaction times for correct responses (atropine 1081 ms, saline 1141 ms, t = 1.15, df = 18).

INTERVAL PRODUCTION

Test Description/Procedure

The Interval Production Task (IPT) evaluates time-interval estimations and is part of the Unified Tri-service Cognitive Performance Assessment Battery (12). The task required each subject to generate a series of time intervals by tapping a finger key (Fig. 13) at a rate of two responses per second (acceptable range was 1-3 per second). The goal of the task was to maintain equal time intervals by tapping as regular a rate as possible. Data were collected across two 3-min trials. The subject tapped with the forefinger of the preferred hand. Intervals were timed from the onset of one response to the onset of the next response. Intervals of less than 10 ms were rejected as spurious input.

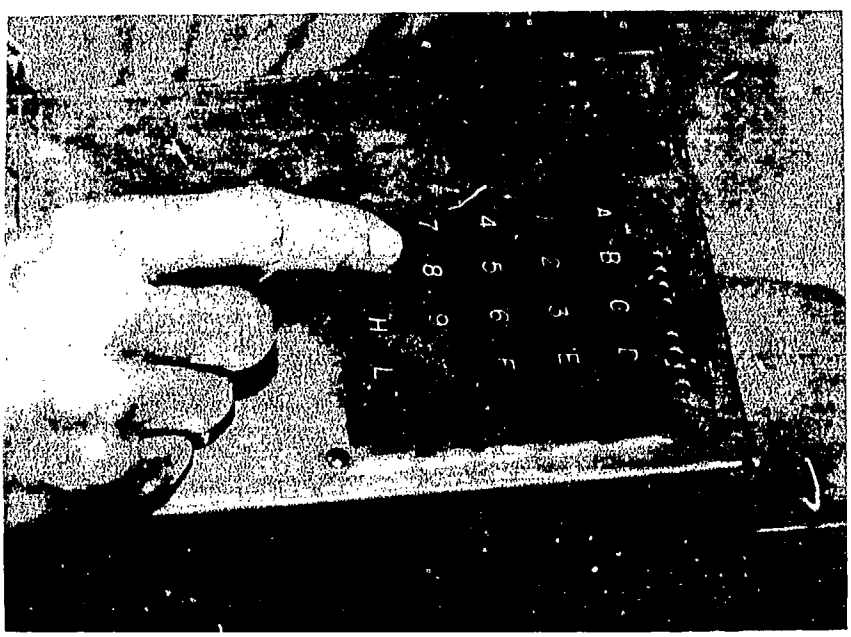

Figure 13. Interval Production Task.

Summary statistics include average interval production, the IPT variability score, and the absolute delta time. The IPT variability score corrects for the partial dependence of error magnitude on interval duration. The following formula calculates IPT variability:

$$V = \frac{N}{T} \sum_{i=1}^{N} \left| \Delta t_i \right|$$

where N is the total number of intervals produced, T is the total time over which data are collected, and t is the difference between successive intervals. A lower IPT variability score indicates more temporally regular tapping and better performance. Typical variability scores range from 10 to 40.

Results - 2 mg

Atropine (2 mg) did not significantly affect a) average interval production (atropine 506 ms, saline 507 ms, t = .09, df = 18), b) IPT variability score (atropine 27.80, saline 29.15, t = .43, df = 18), or c) absolute delta time (atropine 39.39, saline 40.11, t = .16, df = 18).

COLOR VISION

Test Description/Procedure

The Farnsworth-Munsel 100 Hue Test used to evaluate color discrimination abilities (Fig. 14).

Figure 14. Farnsworth-Munsel 100 Hue Test.

Results - 2 mg

Test results with 2 mg atropine were extremely variable (Table 11) and were not significantly different (t = 1.36, df = 11).

TABLE 11. Data from 100 Hue Test.

Subject number	Test score	
	Saline	Atropine
1	39	98
2	95	142
3	32	8
4	27	64
5	43	100
6	36	60
7	105	64
8	56	20
9	68	36
10	8	8
11	47	178
12	0	16

HEART RATE AND BLOOD PRESSURE RESPONSES

Test Description/Procedure

Heart rate and blood pressure responses to atropine and saline were recorded before subjects were injected and at 1 and 4 h following injection.

Results - 2 mg

Mean (± SD) heart rates, systolic blood pressures, and diastolic blood pressure responses to 2 mg atropine are shown in Table 12.

TABLE 12. Heart Rate and Blood Pressure Responses to 2 mg Atropine.

Measure	Drug condition	Preinjection	Postinjection	
			1 hour	4 hours
Heart rate	Saline	69.4 (10.6)	68.5 (10.4)	73.1 (16.5)
	Atropine	70.1 (11.3)	105.2 (10.4)	80.2 (10.7)
Syst press	Saline	123.1 (13.6)	121.6 (12.6)	122.2 (13.4)
	Atropine	120.6 (14.1)	119.2 (13.8)	117.9 (14.7)
Dias press	Saline	73.1 (10.4)	70.4 (9.3)	74.4 (8.8)
	Atropine	74.7 (10.2)	78.9 (12.5)	77.0 (11.9)

Preinjection heart rates were not significantly different (t = .37, df = 13), but both the 1- and 4-h postinjection measurements following atropine were significantly elevated (t = 15.09 and 3.73, respectively, df = 31, p < .001).

Systolic blood pressures for both drug conditions were not significantly different at preinjection (t = .94, df = 31, p = NS) or at 1-h postinjection (t = 1.00, df = 31). There was a significant atropine-induced decrease at 4-h postinjection (t = 2.09, df = 31, p < .05).

Diastolic blood pressures for both drug conditions were not significantly different at preinjection (t = .84, df = 31) or at 4-h postinjection (t = 1.36, df = 31). Atropine induced a significant increase in diastolic pressures at 1-h postinjection (t = 4.37, df = 31, p < .001).

Results - 4 mg

Mean (± SD) heart rates, systolic blood pressures, and diastolic blood pressure responses to 4 mg atropine are shown in Table 13.

TABLE 13. Heart Rate and Blood Pressure Responses to 4 mg Atropine.

Measure	Drug condition	Preinjection	Postinjection 1 hour	Postinjection 4 hours
Heart rate	Saline	82.0 (17.1)	75.1 (11.8)	71.4 (7.9)
	Atropine	78.6 (9.9)	120.6 (15.4)	75.1 (13.4)
Syst press	Saline	122.4 (8.8)	117.0 (10.1)	123.4 (14.0)
	Atropine	125.6 (6.6)	110.0 (9.0)	112.8 (9.4)
Dias press	Saline	69.8 (9.1)	70.0 (10.5)	67.0 (8.7)
	Atropine	69.2 (10.4)	83.1 (9.3)	65.3 (7.2)

Both preinjection and 4-h postinjection heart rates were not significantly different for atropine and saline conditions (t = .85 and .89, respectively, df = 13). The 1-h postinjection heart rates were significantly elevated under the atropine condition (t = 7.55, df = 13, p < 0.001).

Systolic blood pressures were not significantly different at preinjection (t = 1.70, df = 13) but were significantly reduced at 1-h postinjection (t = 2.42, df = 13, p < .05) and at 4-h postinjection (t = 3.18, df = 13, p < .01).

Diastolic blood pressures were not significantly different at preinjection (t = .15, df = 13) or at 4-h postinjection (t = .67, df = 13). Diastolic pressure under atropine was significantly elevated at 1-h postinjection (t = 3.43, df = 13, p < .01).

DISCUSSION

The multidisciplinary test battery at NAMRL is being designed to detect drug-induced performance decrements that could impair flight operations and safety. This preliminary series of tests was used primarily to develop and refine testing methodology, but it also provided limited information on the effect of atropine on performance. For the tests described in this report, the primary performance decrements caused by atropine involved tests of motor movement.

The evidence for atropine disruption of normal motor function follows: 1) rapid fine motor coordination required in the pegboard test was significantly hindered; 2) fine motor coordination needed for compensatory tracking was significantly reduced at 4 mg (but not 2 mg); 3) ambulatory balance (walking) but not static balance was degraded; 4) suppression of nystagmic eye movements was significantly reduced; and 5) the Gaze Function Test, which requires coordinated head and eye movements, was affected by atropine at primarily the shortest exposure time. The effects of atropine on nystagmus, ambulatory balance, and gaze shifts could have been the result of a vestibular system effect versus a motor system effect.

Despite the preliminary nature of this first round of testing, the results are encouraging. We expected that the anticholinergic drug atropine would at some dosage affect the cholinergic motor system. We are delighted that several of our tests were sensitive enough to detect the atropine perturbation of motor function. Now, we must direct our efforts toward interpreting the varying degrees of performance degradation into operationally relevant terms.

RECOMMENDATIONS

A series of control drugs may help establish a comparison "anchor" on which to judge limited drug effects. For the tests reported herein, alcohol (0.10 mg% blood alcohol) could serve as an excellent comparative baseline. A line commander could intuitively relate various alcohol levels and corresponding levels of the motor (or perceptual) impairment to the same levels of motor impairment resulting from selected drug dosages. In effect, we believe that the development of such comparative baselines would contribute significantly to the operational interpretation of drug-induced performance decrements identified by the multidisciplinary test battery described in this report.

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Other Related NAMRL Publications

None are applicable.